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Brief Clinical Report

Congenital Pulmonary Lymphangiectasia and Other Anomalies in a Child: Provisionally Unique Syndrome?

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Congenital pulmonary lymphangiectasis is a rare anomaly that is causally heterogeneous. It can occur as either an isolated finding or one manifestation of several multiple congenital anomaly syndromes. We describe a child with congenital pulmonary lymphangiectasis and other anomalies who likely has a provisionally unique condition.

KEY WORDS: pulmonary anomaly, lung anomaly, multiple congenital anomaly syndrome

INTRODUCTION

Congenital pulmonary lymphangiectasis (CPL) is a rare developmental disorder of the pulmonary lymphatics. The pathologic characteristics are well-delineated, and consist of lymphatic cysts in the subpleural and interlobar connective tissue. This is a typically lethal disorder, with death usually occurring neonatally. CPL is heterogeneous, with most cases sporadic. There have been two case reports of sibs, suggesting autosomal-recessive inheritance in these families [Scott-Emuakpor et al., 1981; Moerman et al., 1993]. CPL has also been associated with multiple congenital anomaly (MCA) syndromes such as Noonan, Ullrich-Turner, and Down syndromes [Moerman et al., 1993].

We describe a male infant with CPL and multiple congenital anomalies, in whom a diagnosis of Fryns syndrome was suggested. However, the overall facial phenotype was not consistent with that described in Fryns syndrome; therefore, we suggest that our patient has a provisionally unique, multiple anomaly syndrome which includes CPL.

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CLINICAL REPORT

B.W. was a male infant born at 34 weeks of gestation to a 25-year-old married white woman. This was the second born child to the nonconsanguineous parents. Prenatal history was complicated by second-trimester severe polyhydramnios, requiring amniocentesis. Prenatal ultrasound study at 32 weeks demonstrated a large right pleural effusion that was tapped for clear fluid, which was lymphatic in origin. Repeat ultrasound study showed a possible left diaphragmatic hernia. The infant was born after spontaneous labor and weighed 2.6 kg (75th centile). Apgar scores were 6 and 7 at 1 and 5 min, respectively. He required aggressive ventilation with high-frequency oscillation and surfactant replacement early in his course. Initial chest radiographic studies indicated a small right pleural effusion with a left diaphragmatic eventration. Because of clinical instability and evidence of persistent pulmonary hypertension of the newborn, plication of his diaphragm was delayed.

Physical evaluation demonstrated a broad nasal bridge, small nose with anteverted nares, small mouth, short philtrum, microretrognathia (Fig. 1), simple ears with attached earlobes, and widely-spaced hypoplastic nipples with a narrow thorax. He was also noted to have small hands (5.25 cm, <3rd centile) (Fig. 2), and feet that were tapered. There were single transverse palmar creases. His testes were descended, but the penis appeared small. Results of head and heart ultrasound studies were normal, except for the right-to-left shunting noted on echocardiogram. Renal ultrasonography showed normal kidneys with mild caliectasis. The palate was intact, and corneal clouding was not present. The karyotype was 46,XY.

This patient remained ventilator-dependent and did not tolerate weaning. Portagen feedings were initiated on the fourteenth day of life. Despite use of this medium-chain triglyceride formula, a chest tube was required to drain a large right pleural effusion. Analysis of the fluid reconfirmed lymphatic origin with triglycerides and 84% lymphocytes. The radiographic appearance remained hazy, with a diffuse reticulogranular appearance that only partially cleared early in his course. With the lack of clinical improvement and consistently hazy congested lung fields without evidence of pulmonary interstitial emphysema, pulmonary lymphangiectasia became the clinical diagnosis of exclusion (Fig. 3). With the suspected CPL and Fryns syn-

Fig. 1 Face of patient. Note small mouth.

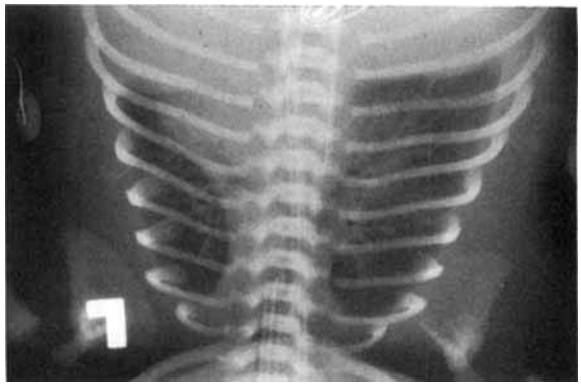

Fig. 3 Chest radiograph. Note elevation of left hemidiaphragm, consistent with documented eventration. Bilateral effusions are present, with only the right clearly visible here.

drome, his parents elected to remove him from ventilator support on day 39 of life. Autopsy was limited to lung tissue analysis.

Microscopic evaluation showed marked distension of pleural and interstitial lymphatics, except in areas obliterated by pleuritis. There was no multinucleated giant-cell response to suggest chronic interstitial emphysema. The pleuritis was marked by a modestly hypervascular, thickened pleura with fibrin deposition, mesothelial cell proliferation, and the presence of histiocytes. The alveolar septa were thickened with fibroplasia, focal collagen deposition, and infiltrate of inflammatory cells. The septal thickening was variable but did not display the acinus-to-acinus variability characteristic of bronchopulmonary dysplasia (Fig. 4).

DISCUSSION

CPL is a rare congenital anomaly which was first described by Virchow [1856]. CPL can be classified into three categories [Noonan et al., 1970]. Group 1 has generalized lymphangiectasis which may include hemihypertrophy, and pulmonary and intestinal involvement. Pulmonary involvement is less severe in this form, and is associated with a better prognosis. Group 2 has acquired dilated pulmonary lymphatics secondary to obstruction of pulmonary venous flow, such as that associated with total anomalous venous return. Group 3 represents patients thought to have a primary developmental defect of the lung lymphatics. Prognosis is poor in this group, with a natural history of early death. Autopsy findings include numerous dilated lymphatic channels in the pleura, interlobar septa, and bronchovascular axes. These fluid-filled cysts, surrounded by loose and excessive connective tissue, create a noncompliant pulmonary parenchyma [Moerman et al., 1993]. Radiographic appearance may be indistinguishable from pulmonary interstitial emphysema or chronic lung disease. CPL can be a first link in a chain reaction, with the initial dilatation of lymph channels being microscopic in nature, with progression leading to weeping of lymphatics and subsequent pleural effusion. Diagnosis is difficult to make as it requires a lung biopsy in a patient who is typically unstable. It may be missed on autopsy, especially if microscopic in nature, because of the collapse of lymphatics when the lung is removed from the thorax [Moerman et al., 1993].

Fig. 2 Hand with thin digits.

Differential diagnoses that may include CPL include Noonan, Ullrich-Turner, and Down syndromes. A recently-described MCA syndrome with persistence of Müllerian derivatives, hepatic failure, postaxial polydactyly, and renal and craniofacial anomalies was also associated with CPL [Urioste et al., 1993]. Bulas et al. [1992] reported on a child with Fryns syndrome who was found to have a cystic hygroma early in gestation. This same patient had diffuse lymphangiectasis with the development of ascites and pleural effusions. The authors noted that previously-published autopsy reports had documented a thick webbed neck in 17 of 25 Fryns syndrome patients, with hydrops. This last possibility was most intriguing, in that our patient had many of the same phenotypic findings as those which have been described in Fryns syndrome. Fryns syndrome is a multiple congenital anomaly syndrome first described by Fryns et al. [1979], and subsequently reported in several other patients worldwide [Aymé et al., 1989; Cunniff et al., 1990; Kershisnik et al., 1991; Langer et al., 1994; Lubinsky et al., 1983; Meinecke and Fryns, 1985; Stratton et al., 1993; Tsukahara et al., 1995]. The manifestations of Fryns syndrome were reviewed recently [Bamforth et al., 1989; McPherson et al., 1993], and include craniofacial manifestations

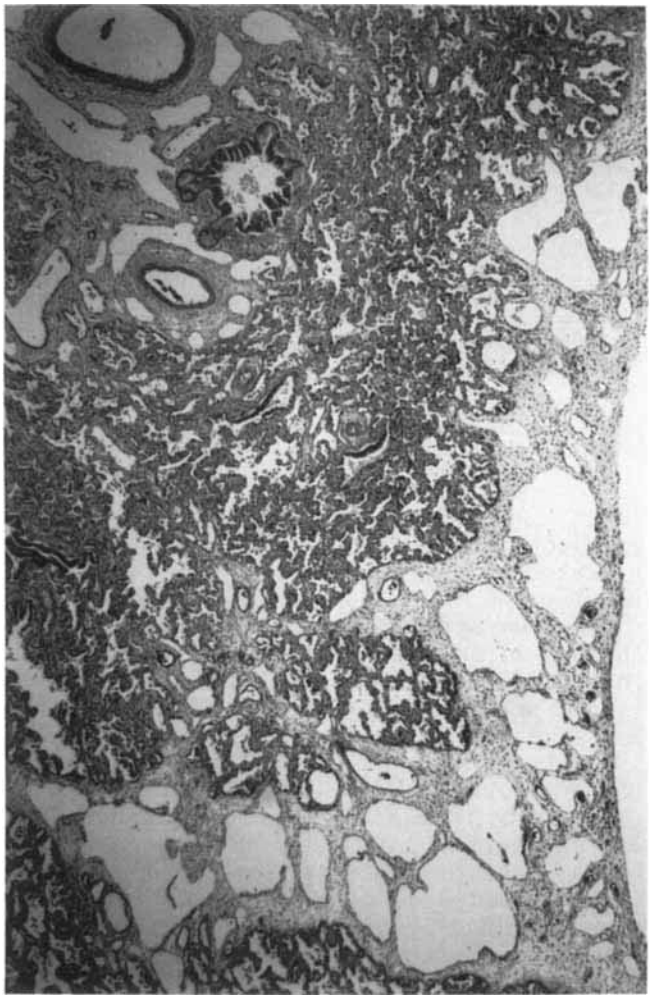

Fig. 4 Section of lung. Dilated lymphatic spaces noted in the thickened pleura, interlobar septa, and bronchovascular axes.

such as "coarse" face, broad flat nasal bridge, macrostomia, microretrognathia, and poorly-modelled ears with attached lobes. Diaphragmatic defects, pulmonary segmentation anomalies, intestinal anomalies (including malrotation and/or atresia), and distal limb and nail hypoplasia also occur. Inheritance is considered autosomal recessive [Cunniff et al., 1990].

There have been several reported instances of chromosome aneuploidy in infants with a Fryns syndrome phenotype [Dean et al., 1991; deJong et al., 1989; Clark and Fenner-Gonzales, 1989; Krassikov and Sekhon, 1990], as well as phenotypic overlap with Pallister-Killian syndrome [McPherson et al., 1993] and Brachmann-de Lange syndrome [Jelsema et al., 1993] (although it is possible that the sibs reported by Jelsema et al. [1993] may in actuality have had Fryns syndrome). These latter reports suggest that phenocopies for Fryns syndrome exist, and that the combination of craniofacial anomalies, distal limb hypoplasia, and diaphragmatic and other defects is not necessarily pathognomic for Fryns syndrome.

However, based on phenotypic analysis, and particularly on the facial appearance in our patient, we conclude that our patient had none of these conditions. We suggest that he had a previously undescribed multiple congenital anomaly syndrome of unknown cause. This condition should be added to the list of syndromes which include CPL in the phenotype.

REFERENCES

Aymé S, Julian C, Gamberelli D, Mariotti B, Luciani A, Sudan N, Maurin N, Philip N, Serville F, Carles D, Rolland M, Giroud F (1989): Fryns syndrome: Report of 8 new cases. Clin Genet 35:191–201.

Bamforth JS, Leonard CO, Chodirker BN, Chitayat D, Gritter HL, Evans JA, Keena B, Pantzar T, Friedman JM, Hall JG (1989): Congenital diaphragmatic hernia, coarse facies, and acral hypoplasia: Fryns syndrome. Am J Med Genet 32:93–99.

Bulas D, Saal H, Allen J, Kapur S, Nies B, Newman K (1992): Cystic hygroma and congenital diaphragmatic hernia: Early prenatal sonographic evaluation of Fryns syndrome. Prenat Diagn 12: 867–875.

Clark RD, Fenner-Gonzales M (1989): Apparent Fryns syndrome in a boy with a tandem duplication of 1q24–31.2. Am J Med Genet 34:422–426.

Cunniff C, Jones KL, Saal H, Stern H (1990): Fryns syndrome: An autosomal recessive disorder associated with craniofacial anomalies, diaphragmatic hernia and distal digital hypoplasia. Pediatr 85: 499–504.

Dean JCS, Couzin DA, Gray ES, Lloyd DJ, Stephen GS (1991): Apparent Fryns syndrome and aneuploidy: Evidence for a disturbance of the midline developmental field. Clin Genet 40:349–352.

DeJong G, Roussouw RA, Retief AE (1989): Ring chromosome 15 in a patient with features of Fryns syndrome. J Med Genet 26:469–472.

Fryns JP, Moerman F, Goddeeris P, Bossuyt C, Van den Berghe H (1979): A new lethal syndrome with cloudy corneae, diaphragmatic defects and distal limb deformities. Hum Genet 50:65–70.

Jelsema RD, Isada NB, Kazzi NJ, Sargent K, Harrison MR, Johnson MP, Evans MI (1993): Brief clinical report: Prenatal diagnosis of congenital diaphragmatic hernia not amenable to prenatal or neonatal repair: Brachmann-de Lange syndrome. Am J Med Genet 47:1022–1023.

Kershisnik M, Craven C, Jung A, Carey J, Knisely A (1991): Osteochondrodysplasia in Fryns syndrome. Am J Dis Child 145:656–660.

Krassikov, N, Sekhon GS (1990): Terminal deletion of 6q and Fryns syndrome: A microdeletion/syndrome pair? Am J Med Genet 36: 363–364.

Langer J, Winthrop A, Whelan D (1994): Fryns syndrome: A rare familial cause of congenital diaphragmatic hernia. J Pediatr Surg 29:1266–1267.

Lubinsky M, Severn C, Rapoport JM (1983): Fryns syndrome: A new variable multiple congenital anomaly (MCA) syndrome. Am J Med Genet 14:461–466.

Meinecke P, Fryns JP (1985): The Fryns syndrome: Diaphragmatic defects, craniofacial dysmorphism, and distal digital hypoplasia. Clin Genet 28:516–620.

McPherson E, Ketterer K, Salsburey D (1993): Pallister-Killian and Fryns syndromes: Nosology. Am J Med Genet 47:241–245.

Moerman P, Van den Berghe K, Devlieger H, Van Hole C, Fryns JP (1993): Congenital pulmonary lymphangiectasis with chylothorax: A heterogeneous lymphatic vessel abnormality. Am J Med Genet 47:54–58.

Noonan J, Walters L, Reeves J (1970): Congenital pulmonary lymphangiectasis. Am J Dis Child 120:314–319.

Scott-Emuakpor A, Warren S, Kapur S, Quiachon E, Higgins J (1981): Familial occurrence of congenital pulmonary lymphangiectasis. Am J Dis Child 135:532–534.

Stratton R, Young R, Heiman H, Carter J (1993): Fryns syndrome. Am J Med Genet 45:562–564.

Tsukahara M, Sase M, Tateishi H, Saito T, Kato H, Furukawa S (1995): Skeletal manifestations in Fryns syndrome. Am J Med Genet 55:217–220.

Urioste M, Rodriguez J, Garcia J, Martin M, Escriba R, Pardo M, Camino, J, Martínez-Frías M (1993): Persistence of Müllerian derivatives, lymphangiectasis, hepatic failure, postaxial polydactyly, and renal and craniofacial anomalies. Am J Med Genet 47:494–503.

Virchow R (1856): "Gesammelte Abhandlungen zur Wissenschaftlichen Medicin." Frankfurt: Meidinger Sohn & Co., p 982.